PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based prospective cohort study from Kerala, India
AUTHORS	Tiwari, Arun Balan, Suma Rauf, Abdul Kappanayil, Mahesh Kesavan, Sajith Raj, Manu Sivadas, Suchitra Vasudevan, Anil Chickermane, Pranav Vijayan, Ajay John, Shaji CK, Sasidharan Krishnan, Raghuram Sudhakar, Abish

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	27-Jun-2021

GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. Most things were fine; I just have one request about the text and some thoughts on the figures. In the abstract, what are the numbers after the +- sign? Standard deviation? 95%CI? something else? Figure 1 - this is a double axis graph and they are not recommended. With so few MISC cases, you might just mark each with, say, a red dot on the line for COVID cases. Or, you might smooth the data more. Or show the ration of MSC to COVID - it depends what you want to emphasize. Supp fig 3 Pie charts are not a good graphical method. With only 3 slices, I would say, just delete this graph and put the numbers in text. If you really want a graph, you can use a Cleveland dot plot. (Pie charts are misinterpreted by our eyes). Peter Flom

REVIEWER	Reviewer name: Dr. Emily Emily Institution and Country: LUMC, WAKZ, Albinusdreef 2, Leiden, 2300 RC, Netherlands Competing interests: None
REVIEW RETURNED	21-Jun-2021

GENERAL COMMENTS	I find this an interesting paper to read and hope to see more data coming from non-western countries on features of MIS-C. It is very important to publish these case series so that differences and similarities of MIS-C between geographical regions / genetic ancestry may become more apparent.

REVIEWER	Reviewer name: Dr. Gladys Palacio Institution and Country: Ricardo Gutierrez Children's Hospital, Gallo, Buenos Aires, Argentina Competing interests: None
REVIEW RETURNED	24-Jun-2021

GENERAL COMMENTS	do not have any other comment about it

VERSION 1 – AUTHOR RESPONSE

Reply to the reviewers' comments:

Serial Number	Original comments of the editor(s) / reviewer(s)	Reply by the author(s)	Changes done on the page number and line number
1.	Formatting amendments: Figure file format - Please note that we do not accept figures in Word document or PowerPoint format. - All figures and images should be supplied as high-quality image files, we recommend PNG, TIFF, or JPG/JPEG. Please ensure images are a minimum of 300dpi and a maximum of 600dpi (resolution).	Thank you for providing an opportunity to improvise the manuscript. Suggested changes in the file format have been made. Word files are converted into PNG files.	Submitted files
2.	Editor in chief comments to author: Abstract Methods add statistical tests used for results included in abstract	Thank you for the suggestion. In addition to the headings of the abstract suggested in the instruction to the authors page, we have added a new heading in the abstract by the name of statistical analysis as per the suggestion.	P 5

		After the addition of statistical details, some editing in the abstract is also done to comply with the word count limit.	
3.	Editor in chief comments to author: Table 2 Echo/cardiac findings would be better as a separate table	Thank you for your input. We have created a separate table no. 3 as per your suggestion. Subsequent table numbers have also been changes.	P 13-17
4.	Editor in chief comments to author: Discussion delete subheading Novelties in the study	Thank you for the suggestion. The subheading is deleted as suggested.	P 24 L 1
5.	Editor in chief comments to author: Delete 1st sentence in this section "This study is among the first to report on medium-term outcomes following MIS-C." Journal style is NOT to describe a study as the first (see instructions to authors)	Thank you for the suggestion. The respective sentence is deleted as suggested.	P 24 L 2
6.	Editor in chief comments to author: Discussion deletes subheadings Limitatio n of the study: and delete numbers in this section - just use text.	Thank you for the suggestion. The subheading is deleted, and the numberi ng is removed as suggested.	P 25 L 1-6
7.	Editor in chief comments to author: Discussion delete "Unanswered questions and future research: 1. What could be the risk factors for the development of MIS-C? 2. Is there any genetic predisposition for MIS-C? 3. MIS-C cases need to be followed for long-term outcomes"	Thank you for the suggestion. The subsection is deleted as suggested.	P 26
8.	Editor in chief comments to author:	Thank you for the suggestion. The sentence is deleted as suggested.	P 29

	What this study adds 1st statement delete "This is the largest cohort of first wave of MIS-C from India"		
9.	Editor in chief comments to author: Delete Supplementary Fig 3	Thank you for the suggestion. The supplementary figure 3 is deleted as suggested and the mention of that has been edited in the main manuscript.	P 17
10.	Editor in chief comments to author: Be cautious in your conclusions	Thank you for your suggestion. We have made few changes in the conclusion to tone down the comparison between western and Indian MIS-C cases as suggested by another reviewer as well.	P 28
11.	Associate editor comments: In addition to the reviewer's comments, please add the statistics results in the table, and when you compare 3 age groups (which you do, which test did you use?) You only mention test for comparison of two groups. If you only perform 2 group tests you need to correct for multiple testing (e.g age group 1 vs 2, 2 vs 3, 3 vs 1, p-value should be 0.05/3, not 0.05)	Thank you for your keen observation and review. In the initial version, we had excluded the age group >12-20 years from the age comparison of statistical analysis as there were only 4 patients in that age group. The mentioned p-values in that version were of the comparison between age group <5 years and 5-12 years only. However, with the understanding of the fact that age group comparisons will put multiple comparisons requiring Bonferroni correction, we have decided to exclude the age group comparisons and keep the tables and relevant results as descriptive only. Hence, in the revised version we have removed the last paragraph on page no. 28 in which compared the <5 years and 5-12 years age group for clinical features.	P 10
12.	Associate editor comments: what are the numbers(numbers) for the cardiac indices in table 2? no(%)? did not all patients get a echocardiogram?	Thank you so much for your keen observation and review. The echocardiography was performed on all the subjects. The numbers (numbers) are no. (%). Cardiac assessment findings are now mentioned in Table 3 (Splitting of table 2	P 16-17

		is done as suggested by the editor). The numbers (numbers) are now explained in the first row of the table 3 itself.	
13.	Associate editor comments: also for the comparison of the ventilated vs non-ventilated patients, please correct for multiple testing, e.g. bonferroni test	Thank you for your expert suggestion. We have applied Bonferroni correction to the suggested section and we have modified the result and conclusion write-up accordingly in the manuscript as well as in the abstract.	
14.	Associate editor comments: the generalization that MIS-C patients from India differ from the US is a bit of an overstatement as your data differ also from other reports from India and you only represent two tertiary hospitals. Please tone down this conclusion	Thank you for the suggestion. We have modified the respective part of the conclusion and have confined the comparison statement to our cohort only.	P 28
15.	Reviewer: 1 Dr. Peter Flom, Peter Flom Consulting Comments to the Author I confine my remarks to statistical aspects of this paper. Most things were fine; I just have one request about the text and some thoughts on the figures. In the abstract, what are the numbers after the +- sign? Standard deviation? 95%CI? something else?	Thank you so much for your kind review. In the abstract, the ± sign after the mean was for standard deviation (SD). The ± sign is removed as per your suggestion, and we have put the SD value in the parenthesis.	P 5
16.	Reviewer: 1 Dr. Peter Flom, Peter Flom Consulting Comments to the Author Figure 1 - this is a double axis graph and they are not recommended. With so few MISC cases, you might just mark each with, say, a red dot on the line for COVID cases. Or, you might smooth the	Thank you so much for your keen observation and kind suggestion. The purpose of the graph in figure 1 is to emphasize that MIS-C cases clustered after the COVID-19 peak in the state. The double-axis was used because the number of active COVID-19 cases were in thousands whereas reported MIS-C cases were at a maximum of two per day.	Submitted images

	data more. Or show the ration of MSC to COVID - it depends what you want to emphasize.	However, in agreement with your suggestion, we have removed the double-axis and the graph is split into A and B sections with the same timeline.	
17.	Reviewer: 1 Dr. Peter Flom, Peter Flom Consulting Comments to the Author Supp fig 3 Pie charts are not a good graphical method. With only 3 slices, I would say, just delete this graph and put the numbers in text. If you really want a graph, you can use a Cleveland dot plot. (Pie charts are misinterpreted by our eyes).	Thank you very much for that suggestion. As per the editor's advice, we have removed supplementary figure 3. The mention of supplementary figure 3 has been removed from the manuscript as well.	
18.	Reviewer: 2 Dr. Emily Emily Comments to the Author I find this an interesting paper to read and hope to see more data coming from non-western countries on features of MIS-C. It is very important to publish these case series so that differences and similarities of MIS-C between geographical regions / genetic ancestry may become more apparent.	Thank you so much for your kind response.	
19.	Reviewer: 3 Dr. Gladys Palacio , Ricardo Gutierrez Children's Hospital Comments to the Author do not have any other comment about it	Thank you so much for your kind review.	

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	19-Aug-2021

GENERAL COMMENTS	The authors have addressed my concerns and I now recommend publication. Peter Flom

REVIEWER	Reviewer name: Dr. Emily Emily Institution and Country: LUMC, WAKZ, Albinusdreef 2, Leiden, 2300 RC, Netherlands Competing interests: None
REVIEW RETURNED	03-Sep-2021

GENERAL COMMENTS	The paper has improved significantly following review.

VERSION 2 – AUTHOR RESPONSE

Reply to the reviewers' comments:

Serial Number	Original comments of the editor(s) / reviewer(s)	Reply by the author(s)	Changes done on the page number and line number
1.	Editor in Chief Comments to Author: Happy for you to exceed word limit to reinsert aim in the introduction	Thank you very much for providing an opportunity to improvise with relaxation in the word limit. The aim is re-inserted into the introduction section.	P6 L 26-30
2.	Associate Editor Comments to the Author: Thank you for the extensive reply and answers Can you please re-insert the aim of the study in the introduction section?	Thank you for suggestion, We have re-inserted the aim in the introduction section as suggested.	P6 L 26-30
3.	Reviewer: 1 Dr. Peter Flom, Peter Flom Consulting The authors have addressed my concerns and I now recommend publication.	Thank you very much for your kind review.	
4.	Reviewer: 2 Dr. Emily Emily, LUMC The paper has improved significantly following review.	Thank you very much for your kind review.	